Familial Q fever clustering with variable manifestations imitating infectious and autoimmune disease

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Abstract

Q fever, caused by *Coxiella burnetii*, can present as an outbreak of acute disease ranging from asymptomatic disease, pneumonia, hepatitis or fever of unknown origin, which can progress to a chronic disease, most frequently endocarditis. The occurrence of Q fever within families is rarely described, and in most cases presents with uniform acute disease manifestations. Here we present a familial cluster of Q fever presenting as highly variable synchronous manifestations in four of five family members, including prolonged fever of unknown origin, asymptomatic carrier state, hepatitis, and chronic endocarditis developing in the absence of previous symptoms. This case series highlights the possibility of Q fever developing in cohabitated individuals with highly variable symptoms masking the common disease etiology. Screening of all exposed individuals, even those not clinically suspected to be infected, may enable to better identify, treat and prevent progression to chronic disease.

Keywords: Anticardiolipin, antiphospholipid, autoantibodies, Q fever, screening
Original Submission: 5 September 2014; **Revised Submission:** 24 December 2014; **Accepted:** 8 January 2015
Editor: D. Raoult
Article published online: 16 January 2015

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Case presentation

A 55-year-old previously healthy male patient was hospitalized due to 2 weeks of daily high-grade fever and elevated liver enzymes. Two weeks before his admission the patient underwent dental transplantation and was treated with amoxicillin for 3 days. Since then and until his referral, the patient suffered daily spiking fever of up to 39°C and weight loss of 6 kg. The patient did not suffer of headache, odynophagia, dyspnea, dysuria, diarrhea, arthritis or rash. The patient's family history revealed two additional cases of prolonged fever, with one family member diagnosed with infectious mononucleosis and the other with fever and hepatitis without identified etiology, which spontaneously resolved.

Vital signs were remarkable for temperature of 38.3°C and tachycardia of 135 beats/min. No other pathologies were noted on physical examination. Laboratory workup revealed elevated sedimentation rate of 60 mm^3/h, mild leukocytosis of 11*10^3 μL with differential count of 80% neutrophils, and normocytic anaemia with haemoglobin levels of 10 g/dL. Mildly elevated liver enzymes were noted with aspartate aminotransferase of 104 U/L (normal range 0 to 35 U/L), alanine aminotransferase of 138 U/L (normal range 0 to 40 U/L), and CRP of 22.8 mg/dL (<0.5 mg/dL). Ferritin levels were 1600 ng/mL (normal range 10 to 300 ng/mL). Multiple blood and urine cultures were repeatedly sterile.

Serological tests for HIV, viral hepatitis, and *Brucella* were negative; *Cytomegalovirus*, *Epstein Barr Virus* and *Herpes Simplex* type 1 and 2 serology indicated past infection; whereas *Parvovirus* antibodies immunoglobulin (Ig) G and IgM were both positive in high titer, compatible with recent infection.

http://dx.doi.org/10.1016/j.cmi.2015.01.005

Immunological workup revealed normal complement levels, positive antinuclear antibodies with FITC intensity (fluorescein isothiocyanate) at the level of 2 on a scale of 0 to 4 (Kallestad, BioRAD), negative cytoplasmic anti-neutrophil cytoplasmic antibodies and perinuclear anti-neutrophil cytoplasmic antibodies, positive anti-smooth muscle antibody with FITC intensity at the level of 2 on a scale of 0 to 4 (Kallestad, BioRAD), elevated anticardiolipin immunoglobulins of both the IgM and IgG fractions, and anti-beta 2 glycoprotein immunoglobulin M. Free serum antibody light chains analysis indicated increased levels of free kappa chains of 21.5 mg/L (3.3 to 19.4 mg/L) and polyclonal gammopathy documented in plasma electrophoresis. These findings raised the suspicion for malignancy, thus further investigation included positron emission tomography–computed tomography that showed pathological focal uptake in the left knee, pleural effusion and a focus between the great thoracic vessels. The later findings did not correlate with findings in transthoracic echocardiogram and transesophageal echocardiogram, which only showed mild to moderate mitral valve regurgitation without vegetation or abscess. Bone marrow biopsy revealed a fibrin ring and epithelioid granulomas, highly compatible with Q fever. A liver biopsy supported the diagnosis demonstrating eosinophilic, plasma cells and neutrophilic infiltrates, microvesicular and macrovesicular fatty changes.

Enzyme immunoassay of Q fever (Immunodot Q Fever, GenBio, CA, USA) was compatible with acute Q fever, as well as serology of Q fever performed by the national reference laboratory using an indirect fluorescence assay. Phase 2 antibodies IgM level was marginal and IgG level was positive at a titer of 1:1600. Phase 1 IgM level was borderline positive and IgG was negative (cutoff for IgG $\geq$ 1:100) (case 1, Table 1, Fig. 1).

Treatment with doxycycline for 2 weeks did not result in any clinical improvement, thus hydroxychloroquine was added, leading to disappearance of fever within 2 days of treatment. Two months later, follow-up blood evaluation indicated normal erythrocyte sedimentation rate, disappearance of autoantibodies and normalization of immunoglobulin levels.

The patient's family was screened for Q fever. Enzyme immunoassay of Q fever (Immunodot Q Fever, GenBio) test of the daughter with fever and hepatitis was negative when performed during her acute disease. After the diagnosis of the index case, serology for Q fever was performed using indirect fluorescence assay, and was this time consistent with acute Q fever. Phase 2 IgM was positive, and IgG titer was 1:400. Phase 1 IgM was positive, but IgG was negative (case 2, Table 1, Fig. 1). This patient was not treated with doxycycline since she was asymptomatic at the time of Q fever diagnosis, with her liver enzymes already within the normal range and no evidence of valvulopathy by transthoracic echocardiography. Follow-up serology showed persistence of the phase 1 IgG at the same titer as at diagnosis, as previously described by Dupont *et al* [1].

The serology of the daughter previously misdiagnosed with infectious mononucleosis (due to the presence of anti-Epstein-Barr virus nuclear antigen antibodies), was consistent with chronic Q fever as phase 2 IgM was positive, IgG was 1:3200 and phase 1 IgM was positive, IgG was 1:1600. (case 3, Table 1, Fig. 1). Consequently this patient, who did not have a predisposing valvular defect, underwent a transesophageal echocardiogram and an obvious small vegetation of 3 mm in size (typical of Q fever) was observed on a mildly thickened anterior cusp of the mitral valve. Because the diagnosis of Q fever endocarditis was definite according to modified Duke criteria [2] and possible according to the suggested revised criteria by Raoult [3], treatment with doxycycline and hydroxychloroquine was initiated and resulted in a rapid decrease of the titers of phase 1 IgG to borderline in 3 months.

A fourth family member, who was asymptomatic, was diagnosed with acute Q fever when IgM phase II antibodies were positive, IgG titer was 1:400, and phase 1 antibodies were negative. Although one cannot exclude that these serological findings are due to persistence of antibodies resulting from unrelated past infection (case 4, Table 1, Fig. 1). The fifth family member was found to be uninfected with Q fever (case 5, Table 1, Fig. 1).

Discussion

The familial clustering presented in this case series highlights three unusual and often neglected aspects of Q fever—a wide range of presentations within close family contacts, the

TABLE 1. Clinical presentations and serology of Q fever of all cases described in the article

Case #	Age	Sex	Presentation	Serology Phase 2	Serology Phase 1	Echocardiography	Treatment
1	55	M	FUO	IgG 1:3200	IgG 1:400	Mild to moderate mitral regurgitation	Doxycycline + hydroxychloroquine 18 mon
2	24	F	Hepatitis	IgG 1:400	IgG: Borderline	Normal	None
3	14	F	FUO	IgG 1:3200	IgG 1:1600	3 mm vegetation, mildly thickened mitral valve	Doxycycline + hydroxychloroquine-still active
4	28	M	Asymptomatic	IgG 1:400	IgG negative	Normal	None
5	48	F	Not infected	IgG negative	IgG negative	NA	NA

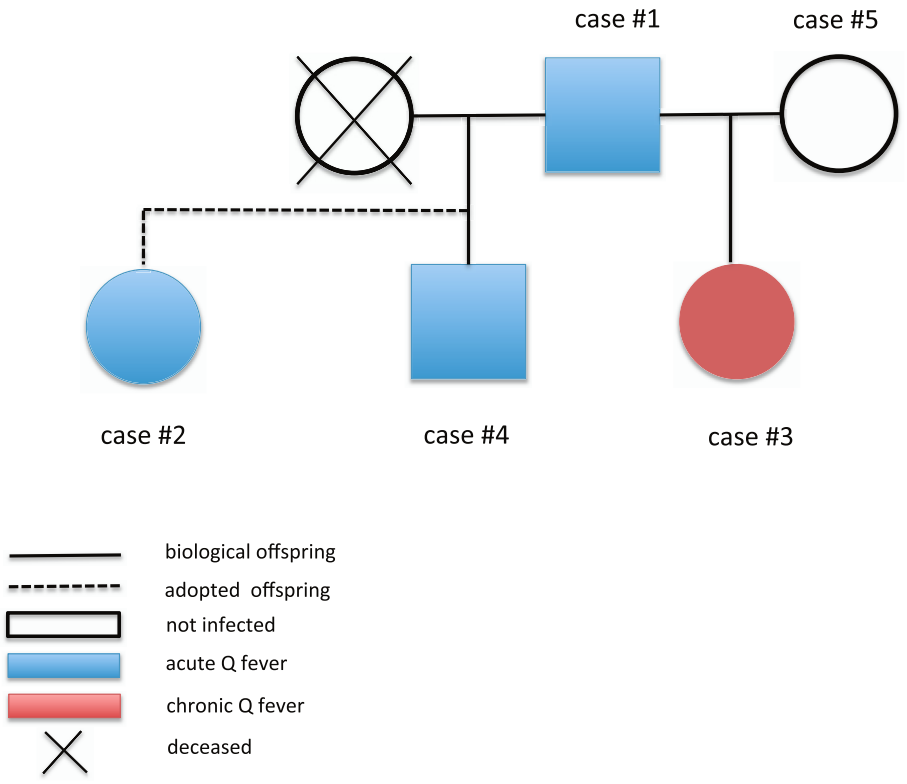

FIG. 1. Family tree describing the clinical presentations of all cases. Circle, female; rectangle, male; cross, previously deceased individual.

presence of multiple autoantibodies masquerading as autoimmune disease and the failure of doxycycline in the treatment of acute Q fever.

Coxiella burnetii is an intracellular bacteria that causes Q fever in humans, mainly through inhalation of aerosolized bacteria from feces, urine or products of conception of infected animals [4,5]. Although it is most commonly described in relation with exposure to domestic mammals, the reservoir includes every domestic or wild mammal, arthropods and birds [6,7]. Horizontal transmission between humans is rarely reported, and uniformly presented with similar clinical presentations of infected family members. Mann *et al* reported Q fever within five members of the same family. The infected family members were living physically apart from each other, and presented within weeks apart. They all presented with pneumonias and were suspected to be infected by a shepherd family member [8]. Sexual transmission of Q fever was identified serologically in 9 Spanish shepherds and their wives, without any other family members infected [9]. Q fever infection can present with a wide range of symptoms from being totally asymptomatic to severe systemic infection, pneumonia and hepatitis [10,11]. It can also present as a chronic disease manifesting mainly as endocarditis, vascular infection, hepatitis, pericarditis and osteomyelitis in specific populations at risk. The main risk factors for the development of chronic infection are vascular grafts, artificial valves, valvulopathies [12], immunosuppression, and pregnancy [13–15]. Only few reports of Q fever clustering in family members were reported in the English literature, transmitted secondary to exposure to common infected cats, dogs and/or pigeons [7,8,16,17]. In all of these cases, the familial clinical presentation was uniform. In contrast to all previous cases, our cluster represents a previously unreported scenario in which close family members had different Q fever clinical manifestations, although very likely infected from a common source—a kitten that was brought home by patient 2. Because the mother cat was killed by a car accident away from the family house, none of the other family members was exposed to it. The fact that some of the infected family members were not genetically associated with each other (e.g. one family member was adopted in her childhood (case 2, Fig. 1), and the other two siblings had different mothers (case 3 and case 4, Fig. 1) may indicate the importance of genetic background in influencing and even driving different Q fever clinical presentations and merits further studies.

Due to the clinical presentation variability, initial misdiagnosis of two of the family members and different family names, the familial connection was initially overlooked. Only epidemiological investigation tied the strings and identified the probable source of infection, a young kitten that was adopted by the family. Otherwise the diagnosis of three members of this family

could have been missed, one of them suffering from chronic disease despite the lack of any risk factor. Although it is recommended that when an outbreak is identified, high-risk groups for chronic disease should be screened [18], we believe that when Q fever is diagnosed, epidemiological investigation is essential and all contacts should be actively allocated and evaluated due to the potential hazardous consequences of infection with *Coxiella burnetii*.

As in the index case presented earlier, nonspecific occurrence of false-positive antibodies in patients may lead to a wrong diagnosis because both the clinical presentation and the serological appearance may mimic multiple viral and autoimmune diseases [19]. In a large retrospective analysis of acute Q fever cases in Israel, positive serology for other infectious diseases was noticed, including elevated IgM levels for *Epstein-Barr Virus*, *Cytomegalovirus*, *Mycoplasma* pneumonia, Parvovirus, *Bordetella* pertussis, *Rickettsia conorii* and *Rickettsia typhi,* noted in 13.8%, 8.3%, 12.12%, 22.2%, 25%, 13% and 21.7% of cases, respectively [20]. False-positive HIV serology also was reported by de la Calle *et al* [21], Morera Montes *et al* [22] from Spain, and Yale *et al* from the United States [23].

Because the immunological reaction in Q fever is robust, the development of autoantibodies in Q fever, as presented in this series, is frequently noted. Antimitochondrial antibodies and anti–smooth muscle antibodies have been described in Q fever, with a prevalence of 33% [20,24]. These autoantibodies were detected in the acute phase (27%) as well as in the chronic phase (38%). The presence of antiphospholipid Ab and anticardiolipin (aCL) in Q fever is a well-recognized phenomenon with estimated prevalence of 81% and 76%, respectively [25]. Recently it was shown by Million *et al* that high levels of aCL correlate to evolution of acute Q fever to endocarditis [26]. It was suggested that this can serve as a surrogate marker for valvulopathies and is predictive of progression to endocarditis in the absence of preventive treatment. In cases without valvular pathology, serum level of aCL > 90 GPL units is considered an indication to perform transesophageal echocardiography [26].

The index case presented with an unusual severely acute Q fever that did not respond to 2 weeks of treatment with doxycycline while the expected time to response is 1.7 to 4 days [10,27]. Slow regression of symptoms in patients with Q fever is reported anecdotally. In a case series of patients suffering from acute Q fever hepatitis accompanied by autoantibodies (smooth muscle antibodies and cold agglutinins), the addition of steroids obtained apyrexia [10,24]. Munckhof *et al* described the recovery of a critically ill patient when rifampin was added after 5 days of intravenous doxycycline [28]. In our case the treatment failure might be attributed to the disseminated disease (hepatic and bone marrow involvement). The fact that *Coxiella burnetii* is an acidophilic bacterium whose metabolism is enhanced at an acidic pH might explain the synergistic effect of hydroxychloroquine that increase the pH in the lysosome [29,30].

In summary, Q fever is a zoonotic disease with different clinical manifestations that can masquerade as autoimmune disease due to uncontrolled autoantibody production. The clinical manifestation of infected individuals is probably related not only to virulence factors in specific clones but also to genetic factors. Because of the potential evolution to chronic disease, we suggest that in case of an outbreak, every exposed individual should be serologically screened and evaluated accordingly.

Transparency declaration

There is no conflict of interest to declare.

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